OBSTETRICS

Maternal obesity and neuroprotective magnesium sulfate

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OBJECTIVE: Given the association between risk of cerebral palsy and children born to obese women, the study aim was to estimate whether maternal obesity is associated with reduced effectiveness of conventional antenatal magnesium sulfate dosing for the prevention of cerebral palsy and death.

STUDY DESIGN: This is a secondary cohort analysis of a multicenter randomized clinical trial completed by the Maternal-Fetal Medicine Units Network. Women were included in the original trial if deemed high risk for preterm delivery in the subsequent 24 hours. The present study included singleton, nonanomalous fetuses that were randomized to and received magnesium sulfate with complete data available. Outcomes between obese (body mass index $\geq$30 kg/m^2) and nonobese women were compared. A secondary analysis of outcomes between morbidly obese (body mass index $\geq$40 kg/m^2) and nonmorbidly obese women was performed. The primary outcome was a composite of cerebral palsy or perinatal death before 15 months corrected age. Secondary outcomes included moderate to severe cerebral palsy or death, any cerebral palsy, moderate to severe cerebral palsy, and death. A logistic regression analysis was used to estimate the odds ratio of each outcome. Based on sample size, exposure rate (obesity) and an outcome rate of 10%, assuming an 80% power and a 0.05 alpha error, this study had sufficient power to detect a 2-fold increase in the primary outcome.

RESULTS: Of 1188 women randomized to receive magnesium sulfate, 806 were included in this analysis. After adjusting for gestational age at delivery, maternal obesity was not associated with an increased risk of cerebral palsy or death in children born to women who received magnesium sulfate. Women with morbid obesity had higher rates of the primary outcome and cerebral palsy in an unadjusted analysis but did not have increased risks after adjusting for gestational age at delivery. In analyses stratified on gestational age, morbidly obese women who delivered after 28 weeks had increased risks of children with cerebral palsy or death and cerebral palsy, although case numbers were small.

CONCLUSION: Among women receiving antenatal neuroprotective magnesium sulfate, maternal obesity is not associated with an increased risk of having a child with cerebral palsy or death.

Key words: magnesium sulfate, neuroprotection, obesity

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In the United States, overweight and obese women constitute greater than half of all pregnant women.[1,2] Obesity is associated with adverse pregnancy outcomes including miscarriage, preterm delivery, the need for cesarean delivery, preeclampsia, and gestational diabetes.[1,3] There is emerging evidence that the inflammatory environment that is present in obese women is responsible for some of the adverse outcomes.[2,3] The inflammatory state of obesity may be an independent risk factor for the development of cerebral palsy in children of obese mothers because the inflammatory environment may increase susceptibility to hypoxic-ischemic injury.[2,4]

Antenatal magnesium sulfate ($MgSO_4$) administered to mothers at risk of preterm delivery reduces the risk of cerebral palsy.[5,6] Magnesium sulfate crosses the placenta rapidly and levels in the neonate are similar to maternal levels at birth.[7] The exact mechanism of neuroprotection is unknown but is likely multifactorial including stabilization of blood vessels and antiinflammatory effects.[5,7,8] It is biologically plausible that there is a minimum amount of magnesium that must reach the fetus for the medication to be effective.

Given that many pharmacological therapies, such as antibiotics, need escalated dosing for obese women because of increased vascular volume and that obesity may be an independent risk factor for cerebral palsy given the proinflammatory state, it is essential to determine whether the standard dose of neuroprotective magnesium sulfate is as effective in obese women. The aim of this study therefore was to determine whether obesity is associated with a

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reduced effectiveness of conventional antenatal magnesium sulfate dosing for neuroprotection, resulting in an increased risk of cerebral palsy and death in children born to mothers who received magnesium sulfate.

Materials and Methods

This study is a secondary cohort analysis of a previously reported multicenter randomized clinical trial. The initial study was completed by the Maternal-Fetal Medicine Units Network and subjects were recruited at 20 centers between 1997 and 2004.[5] All centers and the data-coordinating center received institutional review board approval. This study, based on publicly available deidentified data, was exempt by the Institutional Review Board at the University of North Carolina.

The data collection procedures for the original study have been previously described.[5] Infant follow-up data were obtained at 6, 12, and 24 months of age. All data were edited and validated on a regular basis.

The inclusion criteria and randomization protocol for the initial prospective trial are previously detailed.[5] Briefly, women were included in the initial trial if considered to be at high risk for preterm delivery at 24 through 31 weeks. Women were considered high risk of preterm delivery if they presented with rupture of membranes (22-31 weeks), spontaneous labor with cervical dilation of 4-8 cm, or providers anticipated an indicated preterm delivery within 24 hours.

The primary analysis of the current study included only singleton, nonanomalous fetuses (diagnosed before or after birth) randomized to $MgSO_4$ infusion that received study drug. However, we performed a supplementary analysis stratified on obesity of all patients in the trial (allocated to study drug vs placebo) to help assess whether maternal obesity modified the effect of magnesium sulfate on the risk of cerebral palsy or death.

Magnesium sulfate was administered via a loading dose (6 g over 20-30 minutes), followed by a maintenance infusion of 2 g/h. After 12 hours, if delivery had not occurred and was no longer determined imminent, the $MgSO_4$ was discontinued. If delivery again threatened, the $MgSO_4$ was restarted; if more than 6 hours had passed since the drug was given, the $MgSO_4$ loading dose was repeated upon reinitiating therapy. Retreatment did not occur if open-label magnesium sulfate became indicated for preeclampsia, if a delay in delivery for retreatment would increase risk to mother or fetus, or the gestational age reached 34 weeks.

Study groups in the current study were defined by prepregnancy body mass index (BMI) determined at the time of enrollment. For the primary analyses, BMI of $\geq$30 kg/m^2 was considered obese and was defined as the exposed group. BMI $<$30 kg/m^2 was considered nonobese. The primary outcome was a composite of cerebral palsy (mild, moderate, or severe) or death (stillbirth or death before 15 months corrected age). Secondary outcomes included moderate to severe cerebral palsy or death, any cerebral palsy, moderate to severe cerebral palsy, and death.

Cerebral palsy was assessed and diagnosed at or beyond 2 years of life by an annually certified pediatrician or pediatric neurologist according to strict criteria.[5] Additional secondary analyses compared outcomes in morbidly obese women (defined as BMI of $\geq$40 kg/m^2) with women with a BMI less than 40 kg/m^2. To reduce the chance of masking an association by including overweight women in the nonobese reference group, the analysis for obese women (BMI $\geq$30 kg/m^2) was repeated excluding women with BMI of 25-30 kg/m^2 from the nonobese group.

Similarly, the analysis for morbidly obese patients was repeated excluding overweight and obese women from the nonmorbidly obese group. To assess for interaction between gestational age and obesity or morbid obesity, we also performed analyses stratified on prematurity severity using delivery gestational age categories of less than 28 weeks, 28-32 weeks, and more than 32 weeks. Lastly, we performed a supplementary stratified analysis of the entire clinical trial population comparing the $MgSO_4$ group vs the placebo group for infant outcomes stratified on maternal obesity severity to determine whether obesity was a modifier of the study drug effect on infant neurological and mortality outcomes.

The assessment of obesity as an effect modifier was performed in 2 ways: first, as an intent-to-treat analysis as randomly allocated and then as an as-treated analysis comparing all patients who received study $MgSO_4$ or open-label $MgSO_4$ to patients who received no $MgSO_4$. We tested for evidence of interaction using the Mantel-Haenszel χ^2 test for heterogeneity and logistic regression analysis.

Baseline characteristics between obese and nonobese women were described. Covariates associated with the outcome of cerebral palsy or death were determined using the Student *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 or the Fisher exact test for categorical variables as appropriate. Differences in incidences of the primary and secondary outcomes between study groups were estimated and tested using a χ^2 or a Fisher exact test and the unadjusted relative risks (RRs) with 95% confidence intervals (CIs) were estimated. Effect modifiers and potential confounding factors were identified via literature review and in bivariate analyses.

Logistic regression models were developed to estimate the independent risk of obesity for each outcome, adjusting for confounding factors. All variables considered as potential confounders were included in the initial logistic regression model and were removed one by one while assessing the magnitude of change in the effect size with the remaining covariates. Variables that changed the odds ratio by greater than 10% or were known historically to be confounders were included in the final regression models and adjusted odds ratios with 95% CIs were estimated ($P < .05$ was considered significant). Goodness of fit was assessed with the Hosmer-Lemeshow test for each regression model. Statistical analyses were performed using STATA version